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The Role of Risk Factors in the Prevalence of Urolithiasis in Children (Literature Review)

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Abstract Urinary stone disease (USD) is still topical because it is one of the most common urological diseases and, most importantly, it tends to increase regardless of age. The problem of recurrent nephrolithiasis is also relevant, despite the wide range of treatment options available. Many researchers in recent years have concluded that genetic predisposition to metabolic disorders associated with stone metabolism is the main determinant of urolithiasis, while environmental and dietary factors, which play an important role in the development of urolithiasis in adults, remain insignificant in children. As a multifactorial disease, much attention has been paid by scientists to genetic factors. A method of predicting the occurrence of urolithiasis based on the detection of molecular genetic markers based on DNA analysis has certain and significant advantages.

Keywords Urolithiasis in children, Risk factors, Diagnosis, Genetic factors, Treatment, Prevention

Urinary stone disease (USD) is a common and recurrent disease that occurs in both adults and children worldwide. The epidemiology of urolithiasis is constantly being studied and is under the scrutiny of clinicians as well as health care providers. The incidence of USD in children worldwide has recently shown an upward trend and it is worth noting that the urolithiasis of children differs from that of adults. This is of particular interest and necessity to study the epidemiological processes by age and sex and regionally to determine etiological risk factors for USD, which may be useful in the development of preventive, diagnostic and therapeutic measures to reduce morbidity and initiate early treatment.

The reports of the society of urologists in recent years indicate an increase in prevalence of urolithiasis in the countries where previously the morbidity was rather low - China, Laos, Japan. This necessitates investigations and epidemiological analysis of morbidity figures with the search for risk factors associated apparently not only with endogenous, but also exogenous risk factors in the environment, disturbed ecological situation: presence of calcium salts in drinking water, excessive fatty acid content, etc. It should be noted that over the last 20 years significant advances in the pathogenesis of urolithiasis in children have been made with the introduction of new immunogenetic definitions which have contributed to the understanding of the etiological factors and underpinned the majority of studies aimed at investigating these changes.

Many different factors influence the incidence of USD: race, geographical region, socioeconomic, lifestyle, dietary habits and eating habits.

The literature shows the worldwide prevalence of urolithiasis, but there are countries and regions where the incidence is high and endemic, such as the Middle East, North Africa, and Turkey. The main causative factors are the hot climate, the high rate of consanguineous marriages, and the genetic and racial characteristics that arise. Lack of full epidemiological factors is present in almost every country and therefore the available data varies considerably, possibly due to a lack of methodological approaches as well as proper data collection.

The prevalence and incidence of USD cannot be accurately estimated from hospital admissions and checkups because the data are not a true reflection of reality and therefore an epidemiological study of the population should be performed using well-established methods. This makes the available data on the epidemiology of urolithiasis imperfect as the number of cases in a given period cannot be determined at population level.

USD can be characterized by stone formation over a

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period of time but the disease is asymptomatic and so the patient does not seek treatment for a long time, despite the possibility of a diagnosis.

Studies show that as many as 30% of patients with urolithiasis have to undergo urgent surgical intervention due to renal colic, but the stone may not be present on examination as it has not been detected [10,11,13].

Most investigators have noted the presence of calculi that have been identified on autopsy, suggesting an asymptomatic course in a large number of patients, which also confirms the validity of the prevalence of the disease to be obtained by epidemiological, population-based studies [27,35].

Some authors have suggested that the majority of studies have identified changes in dietary habits and eating habits as playing a role in the development of USD. The works of Chen S., Mai Z., Wu W., Zhao Z., Liu Y., Zeng T., et al. studied the prevalence of USD in Spanish islands and found that over 23% of inhabitants suffered from this pathology, rural residents fell ill more often, which was explained by traditional food habits and lifestyle [15,34].

Most authors indicate that the prevalence of USD is related to the mineral composition of urinary stones, having studied these problems in relation to uric acid (urate) stones, conclusions were made about the prevalence of this type of stones in third world, backward and developing countries, as. In developed countries such as USA, Scandinavia, Belgium, Germany this type of urolithiasis is the least common, from 2.5 to 17%, and in countries such as Sudan, Pakistan, Thailand, Iran from 25 to 43% [14,32].

According to a recent study by Al-Dessoukey A.A., et al, calcium oxalate and calcium phosphate stones with localization in the kidneys and ureters were most common in economically developed countries, while bladder stones consisting of uric acid and ammonium were most common in developing countries [20].

This patchy data proves once again that there is interest in tackling the epidemiology of USD, and an increase in research by scientists who are trying to approach the problem from different angles, analyzing in detail the various risk factors for the development of this pathology.

Most full-scale studies have been carried out in the USA, with numerous findings in men and women aged 30 years and over, which have identified other diseases prevalent in the USA with regional variations and with progression from West to East. The prevalence of USD was 3.7 per 1000 population in North and South Dakota and more than 17-18 per 1000 in North Carolina (South East), with sex differences, with prevalence being higher in males than females and intermediate between whites than blacks, with Asians and Hispanics remaining in between [10,11].

Numerous population-based studies have repeated these patterns, which have subsequently been confirmed in a large number of studies.

There is evidence from the authors Luo D, Li H, Wang K who conducted a study on the prevalence of USD in England and Wales. The study was conducted over a period of 2 years and the prevalence of IBC was 56 per 100,000 in Canterbury, to 15 per 100,000 in Burton-upon-Trent, with a higher incidence in the urban population with a higher socio-economic status, and in urban areas the peak was in the 35-44 age range, which then declined but remained high in males compared to females. In these studies, the authors noted a correlation between the prevalence of USD and mean daily sunlight hours, maximum air temperature and hardness of drinking water, which contributed to the conclusion that climatic factors, geographical location and hardness of drinking water were not important determinants responsible for and contributing to the prevalence of USD [26].

In a study by other authors in England, in a male population aged 49-50 years, more than 16.2% of those questioned had the disease, and in 32.5% of cases the disease was familial, appearing at the age of 30 with a peak at 50 years. The authors also noted the presence of recurrent urolithiasis in 57.6% of patients, with 48% of them having had the disease for 10 years or more after the first symptoms. An interesting fact is that in the majority of the population, 90% of patients with urolithiasis had an independent discharge of the stones, without additional involvement of the healthcare professionals [27].

A French study reported a prevalence of 16.2 per 100,000 population and a prevalence of 900:100,000 over the age of 50 years [2].

In a study of more than 400 000 German adults, the prevalence was more than 5%, and recurrent urolithiasis was found in more than 45% of subjects. In most studies, the prevalence of USD in urban areas was between 2.5 and 4.5% and the lowest in rural areas was 0.3-0.9% [19].

USD occurs in all age groups in the population, the literature suggests that it is most common in adults aged 20-50 years. In the studies by Tiktinsky O.L. et al. 1-3% of patients were most frequent among children and adolescents, and patients with urolithiasis comprised over 50% of all patients in urological hospitals, 25-30% in outpatient clinics, with a 2-2.5-fold increase and 6-6.5% incidence of disability [1,5,10].

Epidemiological studies of the incidence of USD in the United States, according to the National Institute for Health and Nutrition Examination (NHANES), have shown a threefold increase in the incidence between 1976-1980 and 2010, with an increase of 3.2% to 8.8%. The same trend was observed in the UK, where the incidence of urolithiasis increased by 63% (7.14-11.62%) between 2000 and 2010; in Spain, from 4.2% to 5.1%; and in Germany, the increase was modest, from 4% to 4.7% [28,29,32].

As shown by epidemiological studies, Asian countries are endemic for the incidence of USD, with Japan, the PRC and South Korea being the countries with increasing rates. For example, according to Yang Y. the incidence rate in China was more than 6.5%, with characteristic regional dependence and heterogeneity, with a low incidence rate in the northern regions. The highest prevalence was found in South Korea, where the prevalence of urolithiasis was much higher than in other Asian countries, with 457 patients per 100 000

population [18].

The main metabolic disturbances contributing to USD are: hyperurecaemia, hyperuricuria, hyperoxaluria, hypercalciuria, hyperphosphaturia, changes in urine acidification, metabolic disturbances cause renal tubular acidosis, which is important in the pathogenesis. Its development leads to an increase in the degree of ionisation of chemical substances from which stones are formed, and there is a dependence on pH, the level of free ions determining the degree of saturation of the urine. In terms of biochemistry, the solubility of substances leading to stone formation in urine has a correlation with pH. In food, glycine is a precursor of oxalates, hydroxyproline increases the risk of urinary stone formation by promoting hyperuricaemia, calcium combined with hydroxyacetic acid and vitamin C can be metabolised to oxalates in the liver, increasing their concentration in urine, with subsequent formation of oxalate stones. Some studies have shown a combination of lipid and calcium in the intestine leading to the formation of insoluble substances with increased oxalate absorption. Another factor contributing to stone formation is the deposition of crystals at the appropriate urinary pH. Urinary tract stones can form when the basic conditions - concentration of chemical ingredients and appropriate urine pH - are combined. This hypothesis is supported by the high incidence of USD in Southwest and South Asia, where rice is the main food crop, whose carbohydrate catabolism creates a favourable urine environment - an acidic one so essential for stone formation.

According to studies, most scientists think it is mainly due to changes in diet, the global environment and the quality of fluids and food. Other authors have argued that lifestyle changes have been associated with an increased incidence of USD. Other researchers insist in their conclusions that the cause of the dramatic increase in the incidence of urolithiasis in various populations is the increasing incidence of mutations and polymorphism of certain genes [16,23].

The Russian Federation also has some areas endemic for USD - the Caucasus, the Urals, the Volga region and Siberia. Incidence rates remain marginal in countries with a high level of development, income and quality of life, e.g. in western countries there has been an upward trend in the incidence of urolithiasis over the past 15-20 years by more than 37% [4].

In the Russian Federation, USD occurs in 28.3-38.2% of urological diseases, coming second after inflammatory non-specific kidney and urinary tract diseases [3].

According to an epidemiological study of USD in 2016, the number of newly diagnosed cases per 100,000 population was 182.5, an average of -737.5 cases per 100,000 population, which compared with 2005. - The increase was 34%, with a first-time diagnosis of USD at 17.4%. As the authors point out, the total incidence of USD has grown by more than 1.5 times over the last 12 years. According to Türk C., the prevalence of urolithiasis in males and females is 3:1, although a decrease in the gender gap has been observed. Urolithiasis is most common between the age of 40 and 50 years, with a single stone, a bilateral process in 9-17% of cases, but also multiple coral stone lesions have been reported [4,5,8].

If we look at the causative factors and mechanisms that cause the risk of developing USD in the pediatric population, they remain unknown, and there are many hypotheses and theories (about 200) about urinary stone formation [5].

Available data on USD shows that the incidence per 10,000 people in Kyrgyzstan is 4.8, in Ukraine 5.3, Dagestan 2.0, Turkmenistan 2.4, Uzbekistan 3.0, and Russia 5.35 [18]. In the Russian Federation, according to data from the Ministry of Health, the incidence in the younger age group increased from 17.8 to 19.9 per 100,000; in adolescents from 68.9 to 81.7; in adults from 405.2 to 420.0, currently over 540.8.

According to available data, the incidence in Central Asia ranges from 132.9 to 182.6 per 100,000 inhabitants, among natives 14 and newcomers 32; in Uzbekistan the figure is 128.0. In works of Tajik scientists Nusratulloev I. and Nizomov D.S. on stUSDy of prevalence and ecological risk factors of USD development it is noted that morbidity tends to grow, prevalence is more than 250 cases per 100 thousand population. Increase of morbidity is more than 2 times registered in Dushanbe city, with decrease and subsequent sharp increase of more than 150,5 in mountainous-Badakhshan region, eastern districts of high - more than 160 cases per 100 thousand population.

Epidemiological surveys in Central Asia and Kazakhstan have shown that the average rate of USD is 37.6 per 10,000 inhabitants in the Republic and more than 60 per 10,000 in the Mangistau region. According to the Institute of Pathology of Kazakhstan, this region was recognized to be endemic for urolithiasis in the south-west. Studies in this region have shown that the prevalence of this pathology is associated with a dry, hot climate, a shortage of fresh drinking water, high levels of UV radiation, uranium radiation and water salinity [9,10].

As for the studies carried out in Kyrgyzstan, the prevalence of USD in the country has been studied on the basis of admission and hospitalization data. The region of Kyrgyzstan was divided into five climatic-geographical zones, with an incidence of urolithiasis of more than 5 per 10,000 population and more than 5 per 5 per cent in professional examinations. High morbidity was found among the inhabitants of low mountains 5-12 per 10,000 people, the lowest - in high mountain areas from 1 to 5 per 10,000 people. In all likelihood, as the authors think it is due to the natural and climatic conditions of these regions, the characteristics of the living population, who are indigenous, the morbidity was different, in indigenous 4.5 times lower than in non-indigenous.

Thus, the authors referred Kyrgyzstan to the regions where USD is a regional pathology indicating the need for preventive examinations to obtain reliable data on the prevalence of the disease as compared with the data on morbidity and hospitalization.

The prevalence of USD in Turkmenistan was over 25.0 per 100,000 inhabitants, with newcomers twice as likely as

the natives to develop urolithiasis, which may be related to adaptation to the bioclimatic conditions of the region. There was also a difference in the incidence rate between urban and rural residents, with urban residents being 35.0 per 100,000, and rural residents 3 times less, at 12.0. Among factors contributing to stone formation the author pointed out high temperature in the region, hardness and mineralisation of drinking water, gastrointestinal diseases, quality of food and its nature.

The available epidemiological data on the prevalence of USD prove the occurrence of this pathology on all continents, with different levels of incidence. The etiological causative factors are environmental, soil, plant chemistry, salinity of water, climatic conditions, age and gender, occupational and domestic conditions, with endogenous factors including renal disease, urinary tract infections, gastrointestinal disease, bone damage, long-term immobilization, parathyroid hyper function, and genetic predisposition.

In summary, the data show that the morbidity and prevalence of urolithiasis is diverse between different regions of the world and is highly unevenly distributed and varies widely, with countries with a high level of economic development and urbanization leading the way.

Thus, USD is a ubiquitous disease worldwide and its incidence continues to increase steadily. Urolithiasis is considered to be a polyethiological disease with endogenous and exogenous risk factors.

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